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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/555,780	11/17/00	GRAS-MASSE	H 1091/2 PCT/U

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EXAMINER	
FOLEY,S	
ART UNIT	**PAPER NUMBER**
1648	15

DATE MAILED: 07/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/555,780	GRAS-MASSE ET AL.	
	Examiner	Art Unit	
	Shanon A. Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *8 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-11 and 13-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Election/Restriction

Applicant's election without traverse of species of CTL determinants from HIV and the species election of the lipoprotein GAG 253 in Paper No. 9 is acknowledged. Claims 8 and 12 are withdrawn from consideration, due to non-election of the invention. Claims under consideration are 1-7, 9-11, 13-24, to the extent that they read upon the elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9-11, 13-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a mixture of micelles or micro-aggregates that comprise two different lipopeptides. It is unclear whether or not both lipopeptides are contained in a micelle or if each micelle contains one of the lipopeptides, which are brought together in a mixture.

Claim 13 is drawn to inducing a "specific immune response" with the micelles. It is unclear what is intended by a "specific immune response" because the lipoproteins are directed against two types immune responses, the CTL and the T helper. Is the claim drawn to a specific immune response against a specific antigen?

Claim 18 is drawn to nuclear magnetic resonance controlling the dispersal of lipoproteins. It is unclear what is intended by this phrase, since NMR is not conventionally known to facilitate dispersing or mixing.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 14, 16, and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a vaccine composition of micelles that comprise a lipoprotein comprising a CTL antigenic determinant from HIV GAG 253 and lipid units and a helper antigenic determinant and lipid units in a vaccine composition. Claim 20 is drawn to a method of immunizing against this composition. The invention is to drawn to a composition that would be used to evoke a response in the same antigen-presenting cell (APC) to the two antigenic determinants corresponding to a CTL and a helper response.

In order for a treatment method to meet the legal requirements for patentability, the method must be effective in treating or preventing the indicated disease conditions. Where there is reason to doubt the method's effectiveness, and there is no actual working example demonstrating effectiveness, an applicant can be required to provide evidence to substantiate the assertions of effectiveness. The term "vaccine", implies a preventative treatment against disease, see the dictionary citation provided. There is no working example of the treatment method

demonstrating a prophylactic effect of the composition in an individual or animal model against HIV. The examples are limited to antibody responses generated in normal individuals upon administration of the micelle compositions, see pages 25-28. There were also examples of *in vitro* proliferation experiments, which were shown to be limited to PBMC proliferation, see page 30, second paragraph through page 32. The paragraph summarizing the proliferation experiments on page 32, lines 15-22, data indicates that there is insufficient evidence to predict which lipoprotein will have a proliferative effect due to the different responses to the different lipoproteins in different individuals. PBMC's comprise a vast number and type of lymphocytes. It is well known in the art that HIV infection results in a depletion of CD4+ T-lymphocytes, see the abstract of Vergis et al. There is no data in the disclosure indicating that a proliferative response in CD4+ T cells would be a beneficial treatment in an individual with HIV. Kornbluth teaches that activating antigen presenting cells leads to increased CD4+ cell activation, which also leads to an increase in HIV replication in these cells, see the abstract.

Therefore, it is concluded that there is insufficient to convince one skilled in the medical arts of the composition's effectiveness as a vaccine. Because of the lack of guidance in the application, the lack of working examples, and the nature of this invention, it is concluded that undue experimentation would be required to meet the enablement requirements for this invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 9-10, 13-17, 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stuhler et al. and Sastry et al. and Sugimoto et al.

The claims are drawn to a composition of mixed micelles comprising a lipopeptide with a a CTL antigenic determinant from HIV and a second lipopeptide comprising a helper T antigenic that is hemmagglutinin or PADRE determinant. The lipopeptides are two palmitic acid chains linked to lysine. The micelles are dissolved in a solution of acetic acid.

Stuhler et al. teaches a critical linkage of epitopes for helper and CTLs on the surface of one antigen-presenting cell (APC), see the abstract and the introduction. Stuhler et al. were able to activate a complex of cell types, APC, helper, and CTLs by using HIV-gag as the CTL epitope and keyhole limpet hemocyanin (KLH), pigeon cytochrome C, and tetanus toxoid (TT) were used as a source of helper epitopes, see the materials and methods and the results section.

Stuhler et al. does not teach using HA as a helper epitope. However, it is well known in the art that KLH can be substituted by HA because of the similarity in immune response achieved with both, see the abstract of Sugimoto et al. as evidence.

Stuhler et al. does not teach conjugating the CTL epitope to the helper epitope by palmitic acid residues in a micelle composition. However, Sastry et al. teaches a method of eliciting cell-mediated immunity with micelles comprising short peptide sequences of HIV envelope protein gp160 with two palmitic residues attached to the amino-terminal lysine. Sastry et al. generates these micelle compositions by dissolving the peptides with the palmitic residues attached in acetic acid, see the abstract and "peptide polymers" on page 700.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the method of stimulating helper, CTL, and APC immune responses by combining the helper and CTL epitopes taught by Stuhler et al. in the micelle composition taught by Sastry et al. because the linked micelle epitopes would contact the same APC at the same time and the epitopes would not require a carrier molecule. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed composition and specific immune response to HIV-gag because Stuhler et al. successfully stimulates all three cell types in an immune regulatory cluster to an HIV-gag-peptide by stimulating the CTL and helper epitopes on one APC. Sastry et al. teaches a method of successfully stimulating an immune response to HIV-gag by combining the short peptide sequence in a micelle configuration. Therefore, the invention as a whole would have been prima facie obvious at the time the invention was made, absent unexpected results.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stuhler et al. and Sastry et al. and Sugimoto et al. as applied to claims 1-7, 9-10, 13-17, 19-24 above, and further in view of Kramer et al.

Neither Stuhler et al. or Sastry et al. or Sugimoto et al. teach gag 253 sequence of SEQ ID NO: 6. However, Kramer et al., see the sequence alignment provided by the Geneseq database. Kramer et al. further teaches that this sequence is immunogenic and that it can be used in detection assays and pharmaceutical compositions, see the excerpt provided with the sequence alignment. One of ordinary skill in the art at the time the invention was made would have been motivated to use this protein for its immunogenic properties taught by Kramer et al. One of ordinary skill in the art would have had a reasonable expectation of success in using this peptide

in the method of generating a simultaneous a three-way immune response taught by Stuhler et al. because Sastry et al. teaches that micelle compositions is the preferred technique for using synthetic peptides in vaccine compositions.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stuhler et al., Sastry et al., Sugimoto et al., and Kramer et al. as applied to claims 1-7, 9-11, 13-17, 19-24 above, and further in view of Shapiro et al.

The claim is drawn to using nuclear magnetic resonance (NMR) in the preparation of micelle compositions.

Neither Stuhler et al., Sastry et al., Sugimoto et al., nor Kramer et al. teach using NMR in the preparation of micelle compositions.

However, Shapiro et al. teaches the use of two-dimensional magnetic resonance to aid in analyzing the conformation of micelle/peptide-receptor interactions. One of ordinary skill in the art at the time the invention was made would have been motivated to utilize two-dimensional NMR to facilitate the interaction between the targeted APC and the micelle. One of ordinary skill in the art would have had a reasonable expectation of producing the claimed invention because conformational data from NMR can be readily analyzed from the known CTL/helper epitope sequences taught by Kramer et al. and Sugimoto et al. and the receptors on the APC surface used to stimulate the three-way immune cluster taught by Stuhler et al.

Therefore, from the teachings in the references, the invention as a whole would have been prima facie obvious at the time the invention was made, absent unexpected results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 7:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
June 26, 2001

JAMES HOUSEL 7/2/01
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